wherein -LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -$(CH_2)_bC(O)$- where b is an integer from 1-5, a diester diradical of the formula -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone;

wherein -G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl[,] ; and

wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.

15. (Amended) The adhesive composition of claim 1 wherein -LM- is a diester diradical of the formula[,] -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

17. (Twice amended) A method of making a tissue adhesive consisting of the step of forming a mixture of

i) a first aqueous mixture of about 20-60 wt/vol % serum albumin in about 0.01-0.25 molar buffer at a pH in a range of about 8.0-11.0,

ii) a second aqueous mixture of about 50-800 mg/ml of a crosslinking agent having a molecular weight in a range of about 1,000-15,000, wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein -PEG- is a diradical fragment represented by the formula

-O-$(CH_2$-CH_2-O-$)_a$-

where a is an integer from 20-300;

wherein -LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -$(CH2)_bC(O)$- where b is an integer from 1-5, a diester diradical of the formula -C(O)-$(CH2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone; and

wherein -G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl[,] ; and

wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.

37. The method of claim 36 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-$(CH_2$-CH_2-O-$)_a$-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -$(CH_2)_bC(O)$- where b is an integer from 1-5, a diester diradical of the formula -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected

from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

71. The method of claim 70 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-C(O)-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

103. The method of claim 102 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -$(CH_2)_b$C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

138. The method of claim 137 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-$(CH_2$-CH_2-O-$)_a$-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -$(CH_2)_b$C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

~~165~~ 13. A method of treating tissue to prevent or control air or fluid leaks comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20-60 wt/vol % and a crosslinking agent at about 50-800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in a range of about 1,000-15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength greater than about 10 mm Hg.

~~180~~ 35. The method of claim ~~179~~ 34 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-C(O)-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

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D10 185. The method of claim 180 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

D11 49 194. The method of claim 193 wherein the air leak is in a pulmonary system.

D12 50 195. A method of treating tissue to prevent formation of an adhesion comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20-60 wt/vol % and a crosslinking agent of about 50-800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in the range of about 1,000-15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength greater than about 10 mm Hg.

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D13 212. The method of claim 211 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-(CH_2-CH_2-O-)$_a$-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH_2)$_b$C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-(CH_2)$_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-(CH_2)$_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH_2)$_c$-C(O)-, or -R-C(O)-O-(CH_2)$_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

215. The method of claim 212 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

225. A method of treating tissue to bind layers of tissue together comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20-60 wt/vol % and a crosslinking agent at about 50-800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in the range of about 1000-15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength of greater than about 10 mm Hg.

242. The method of claim 241 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-C(O)-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

245. The method of claim 242 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

258. A method of treating tissue comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20-60 wt/vol% and a crosslinking agent at about 50-800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in a range of about 1000-15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength greater than about 10 mm Hg.

268. The method of claim 258 wherein the matrix has a burst pressure of about 34 mmHg or greater.

269. The method of claim 268 wherein the matrix has a burst pressure of about 90 mmHg or greater.

270. The method of claim 269 wherein the matrix has a burst pressure of about 130 mmHg or greater.

275. The method of claim 274 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10

and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

278. The method of claim 275 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

290. The method of claim 289 wherein the air leak is in a pulmonary system.

318. The method of claim 317 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-$(CH_2$-CH_2-O-$)_a$-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -$(CH_2)_b$C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

321. The method of claim 318 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

332. The method of claim 331 wherein the air leak is in a pulmonary system.

351. The method of claim 350 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-C(O)-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

354. The method of claim 351 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

382. The method of claim 381 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-C(O)-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

385. The method of claim 382 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

409. The method of claim 408 wherein the matrix has a burst pressure of about 34 mmHg or greater.

410. The method of claim 409 wherein the matrix has a burst pressure of about 90 mmHg or greater.

411. The method of claim 410 wherein the matrix has a burst pressure of about 130 mmHg or greater.

416. The method of claim 415 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -$(CH_2)_bC(O)$- where b is an integer from 1-5, a diester diradical of the formula -$C(O)$-$(CH_2)_c$-$C(O)$- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -$C(O)$-O-$(CH_2)_d$-O-$C(O)$- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-$C(O)$-$(CH_2)_c$-$C(O)$-, or -R-$C(O)$-O-$(CH_2)_d$-O-$(C)O$- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

419. The method of claim 416 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

431. The method of claim 430 wherein the air leak is in a pulmonary system.

REMARKS

Claims 1-440 are pending in the application. As explained below, claims 1, 15, 17, 37, 71, 103, 138, 163, 180, 183, 194, 195, 212, 215, 225, 242, 245, 258, 268, 269, 270, 275, 278, 290, 318, 321, 332, 351, 354, 382, 385, 409, 410, 411, 416, 419, and 431 have been amended. No new matter has been added.

Claim 1 has been presented with additions to the claim underlined, and deletions bracketed, in accordance with 37 C.F.R. 1.121(b). Applicants thank the examiner for pointing out that the phrase at line 18, "d is an integer from 2-10", and the word "and" that occurred after "tresyl" were omitted in the amendment filed December 20, 2000. These omissions were inadvertent. The text appears in the claim above, as it was intended to appear in the claim throughout prosecution of this reissue application.